consisting of: VSAF (SEQ ID NO:5), VSAFI (SEQ ID NO:51), VSAFIG (SEQ ID NO:52), RVSAF (SEQ ID NO:53), RVSAFI (SEQ ID NO:54), RVSAFIG (SEQ ID NO:55), WRVSAF (SEQ ID NO:56), WRVSAFI (SEQ ID NO:57) and WRVSAFIG (SEQ ID NO:58).

REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1-20, 27-43, 46-49, 52-55 and 58-61 are pending. Claims 9-10 and 14-20 stand withdrawn as allegedly being drawn to a non-elected species. Claims 2-7, 27-30, 33, 35, 40, 46, 52, and 58 have been amended solely for editorial purposes or to more clearly define the subject matter encompassed by Applicants' invention. Support for these amendments can be found throughout the specification and within the originally filed claim set. No new matter has been added.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

(1) Claims 1-4, 5-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In particular, the Action asserts that the specification is not enabling for the current claim scope because it does not disclose the sequence identity of CAR containing peptides that actually reduce cell adhesion in the disclosed example, nor the 9 amino acid CAR sequence used to make the antibodies that have cell adhesion modulating activity as disclosed in Examples 2 and 4, therefore, there is no clear guidance that an agent comprising SEQ ID NO:1 is capable of modulating claudin-mediated processes, such as cell adhesion. The Action further asserts that there is no predictability that the CAR sequence (based on an alignment with other mammalian claudins) would confer the biological activities such as cell adhesion to an agent comprising the CAR sequence because the specification does not disclose where the biological activity of cell adhesion of the claudin resides within SEQ ID NO:1. Additionally, the Action alleges that there is no clear guidance as to the minimum number of amino acids from the deduced consensus amino acid sequence for a

claudin CAR sequence (SEQ ID NO:1) necessary to modulate claudin-mediated processes, such as cell adhesion. Finally, the Action concludes that there is insufficient guidance as to the effect of cyclization of a claudin CAR sequence on its functions, including cell adherence, and that making and using the claimed agent is complex and well outside the realm of routine experimentation.

Applicants respectfully traverse these grounds for rejection and submit that the presently pending claims are adequately enabled. As an initial matter, Applicants wish to point out that an assertion within a specification is presumed to be correct. In order to challenge this presumption, the Examiner bears the initial burden of providing evidence showing that a person of ordinary skill in the art would reasonably doubt the disclosure. *In re Brana,* 34 U.S.P.Q. 2d 1436, 1441 (Fed. Cir. 1995). In the absence of such evidence, Applicants are not required to provide further evidence of the truth of the disclosure, and a claim that corresponds in scope to the disclosure of the specification must be taken to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.; In re Marzocchi,* 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

Within the specification, Applicants have disclosed that claudin CAR sequences comprising 3-16 amino acid residues linked by peptide bonds can be used to modulate cell adhesion mediated by claudin molecules. Any peptide that comprises this sequence may perform this function. Further, such function can be readily confirmed using the assays provided within the specification. Accordingly, Applicants believe that all of the peptides recited within claims 1-4 and claims depending therefrom are fully enabled by the specification. Moreover, Applicants respectfully submit that the identity of the claudin CAR sequences are set forth within the specification at *e.g.*, page 16, line 28 through page 19. However, solely in order to expedite prosecution, Applicants have amended the claims, by canceling claim 1, such that all the pending claims now specify that the peptide sequence is derived from the consensus sequence (SEQ ID NO:1).

As noted above, the specification is presumed enabling without evidence to the contrary. Accordingly, Applicants respectfully submit that one of skill in the art could readily predict that a CAR sequence derived from SEQ ID NO:1 would have the requisite biological activity. Further, the currently pending claims require at least five contiguous amino acids of the eight amino acid sequence set forth in SEQ ID NO:1. Given the teachings of the specification,

including the assays described therein for testing peptides, one of ordinary skill in the art would readily conclude that the claimed peptides would have the asserted activity. In the instant application, Applicants have taught a specific claudin CAR consensus sequence. Armed with this information and given the prior teachings of these inventors in U.S. Patent No. 6,031,072, it would be apparent to those of ordinary skill in the art of cell adhesion that mimicking this consensus sequence can have dramatic affects on cell adhesion. In the aforementioned Patent, peptides comprising the sequence His-Ala-Val within a cyclic peptide ring that contains 4-15 amino acid residues was found fully enabled. The teachings present in the instant application are similarly enabled and, as noted above, given the instant specification and teachings of the prior art, such as the '072 patent, those of ordinary skill in the art of cell adhesion would readily conclude that sequences at least as short as the four amino acid constructs claimed in the '072 patent would have cell adhesion modulating affects. Accordingly, as the presently pending claims comprise at least five amino acids of the eight amino acid consensus sequence (SEQ ID NO:1) those of skill in the art would find the instant specification and presently pending claims fully enabled due to the predictability of success. Lastly, Applicants submit that there is no basis for presuming that the activity of a peptide would be significantly affected by cyclization as is further evidenced in the aforementioned '072 patent. If the Examiner questions the accuracy of Applicants' disclosure, Applicants request that the Examiner provide support for this rejection, in the form of references or a declaration, in accordance with 37 C.F.R. §1.107(b).

Accordingly, Applicants respectfully submit that the disclosure of the instant specification provides sufficient disclosure to teach a person of skill in the art how to use the claimed invention and that no undue experimentation is required to practice the invention. Therefore, Applicants respectfully request that these grounds for rejection be withdrawn.

(2) Claims 1-4, 5-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not adequately described in the specification. In particular, the Action asserts that the instant claims are drawn to a cell adhesion modulating agent, comprising a claudin CAR sequence, which is disclosed as comprising a consensus sequence of eight amino acids (SEQ ID NO:1) of which three amino acids are independently selected. Thus, the Action asserts that it is unclear from the disclosure

whether the "independently selected" amino acids must be present in an equivalent position as one of the sequences used to derive the claudin CAR consensus, or if other sequences may be substituted. Additionally, the Action alleges that the minimum length of a claudin CAR sequence is unclear. Finally, the Action concludes that the specification does not adequately describe what sets apart claudin sequences as a genus from non-claudin sequences.

Applicants respectfully traverse this ground for rejection and submit that the disclosure of the instant specification is commensurate with the scope of the claims. In response to the allegations of the Action, Applicants respectfully submit that one of ordinary skill in the art upon reviewing the specification would conclude that the independently selected amino acids may be any amino acid and that these amino acids must be present at the equivalent positions. Applicants submit that this is clear from the specification and is exemplified at *e.g.*, page 18, Table I which depicts representative sequences in this regard. Accordingly, Applicants respectfully submit that the specification satisfies the requirements under 35 U.S.C. § 112, first paragraph, and request that the rejection be withdrawn.

(3) Claims 33-34 and 38-39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In particular, the Action asserts that while the specification provides enablement for the CAR sequence of the cell adhesion molecules (encompassing SEQ ID Nos: 25 and 26), and for agents comprising an antibody or antigen-binding fragment thereof, it does not reasonably provide enablement for a cell adhesion modulating agent comprising any CAR sequence or any other specific sequence, that is bound by any adhesion molecule, nor any antibody or antigen binding fragment that specifically binds any CAR sequence that is bound by any adhesion molecule, other than those disclosed in specification. The Examiner also asserts that the scope of the claims is not commensurate with enablement provided by the disclosure with regard to the large number of cell adhesion molecules, including any number of other extracellular matrix proteins as recited in claim 34.

Applicants respectfully traverse this ground for rejection and submit that the disclosure of the instant specification is commensurate with the scope of the claims and that no undue experimentation is required to practice the invention. In this regard, Applicants submit that the specification teaches that a variety of other sequences may be combined with claudin

CAR sequences to achieve a desired response. See, *e.g.*, page 28, line 6-16 and page 50, line 27 through page 51, line 13. As those of skill in the art can readily make and use a claudin CAR as set forth in SEQ ID NO:1 and combine such a sequence with any other cell adhesion recognition sequence, Applicants respectfully submit that the presently pending claims are adequately enabled. If the Examiner has specific art in mind that would counter this teaching, she is respectfully requested to make such art of record. Thus, in the absence of art demonstrating that those of ordinary skill could not make and use such agents, Applicants respectfully request that the Examiner withdraw these grounds of rejection.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

(1) Claims 2-7 and 27-39 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, claims 27-39 have been rejected as being dependent upon canceled claims 24-26. Applicants thank the Examiner for noting this informality. Accordingly, Applicants have now amended claims 27-30, 33, and 35 such that they no longer refer to canceled claims 24-26. Withdrawal of this rejection is now respectfully requested.

(2) Claim 33 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the Examiner believes that the phrase "...sequence that is bound by an adhesion molecule..." is unclear in how a molecule can bind to a sequence.

Applicants respectfully traverse this rejection. Applicants are unclear as to the basis of this rejection as it appears clear that the sequence is a cell adhesion recognition sequence located on a polypeptide and is bound by a polypeptide other than a claudin. If the concern is that the term molecule is ambiguous, Applicants submit that this term within the context of the claim refers to a cell adhesion polypeptide. The term adhesion molecule is used throughout the specification, including page 1, line 29-30, page 22, lines 14-17, and page 28, line 6-9 to name a few. Accordingly, Applicants respectfully submit that exchanging the term molecule with another term would result in discontinuity with the specification. As Applicants believe that this term is adequately definite as indicated above, Applicants respectfully request that this ground for rejection be withdrawn.

(3) Claims 5 and 6 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the Action asserts that the recitation of an agent as a peptide ranging in size from 3 to 50 amino acid residues or from 4-50 amino acid residues, respectively, is indefinite since claims 2, 3 and 4 encompass 5, 7, and 8 consecutive amino acids residues of SEQ ID NO:1, respectively.

Applicants thank the Examiner for noting this informality. Accordingly, these claims have now been amended to be commensurate in scope with the claims from which they depend. Applicants thus submit that this ground of rejection has been obviated and request its withdrawal.

(4) Claims 2-7 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the Action asserts that the phrase "independently selected amino acid residues" is unclear as to which specific amino acids are encompassed.

Applicants respectfully traverse this rejection. As noted above, Applicants respectfully submit that one of ordinary skill in the art upon reviewing the specification would conclude that the independently selected amino acids may be any amino acid and that these amino acids must be present at the equivalent positions as depicted in SEQ ID NO:1. Applicants submit that this issue is clear from the specification and further exemplified at *e.g.*, page 18, Table I which depicts representative sequences in this regard. Accordingly, Applicants respectfully submit that this ground for rejection has been overcome and thus request its withdrawal.

REJECTIONS UNDER 35 U.S.C. § 102(B)

(1) Claims 1-3, 5-7 and 35 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ruoslahti *et al.* (U.S. Patent No. 5,627,263, 1997). In particular, the Action asserts that Ruoslahti *et al.* teach a nonomer sequence of CRGDSFVGC, comprising at least 5 and 7 consecutive amino acids of SEQ ID NO:1.

Applicants respectfully traverse this ground for rejection. The sequence set forth in Ruoslahti *et al.* comprises an RGD cell adhesion sequence within the consensus sequence.

While Applicants believe that such a sequence would be dominated by RGD specific binding and not predominately claudin specific, nevertheless, Applicants have amended the claims to indicate that an RGD sequence is not present within the consensus sequence. Accordingly, Applicants submit that this ground for rejection has been overcome.

(2) Claims 2, 35 and 40 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bult *et al.* ("Complete Genome Sequence of the Methanogenic Archaeon, *Methanococcus jannaschii*," *Science 273*:1058-1073, 1996). In particular, the Action asserts that Bult *et al.* teach a 47mer protein that comprises the sequence IYSYX, comprising at least five consecutive amino acids of SEQ ID NO:1.

Applicants respectfully traverse this ground for rejection. As an initial matter, Applicants note that the Bult *et al.* reference merely describes the entire genome sequence of the prokaryotic organism *Methanococcus jannaschii* and depicts many predicted open reading frames. Some of these open reading frames have been predicted to be related to certain known proteins while others have not. The specific sequence cited by the Action is defined by no more than a number (*i.e.*, MJ0820). Further, there is no indication that the sequence is correct or that this is actually a functional open reading frame. Moreover, there is absolutely no indication that the sequence is functional as cell adhesion molecule. Accordingly, without more this hypothetical polypeptide cannot anticipate the claimed compounds as Bult *et al.* does not teach one how to make and use the polypeptide for any purpose whatsoever, let alone as a cell adhesion modulating agent.

The premise that a reference must be enabling to be proper anticipatory prior art is firmly established in the patent law. To this end the several cases note that the mere naming of a compound in a reference, without more, cannot constitute a description of the compound and thus is not "described in a printed publication" within the meaning of 35 U.S.C. § 102(b). See, *e.g., In re Wiggins*, 179 U.S.P.Q. 421 (C.C.P.A. 1973). In later case law, the Board of Patent Appeals and Interferences noted that a reference itself must have an enabling disclosure to be used as a proper reference and that Section 102(b) of 35 U.S.C. has been interpreted as requiring the description of the invention in a publication to be sufficient to put the public in possession of the invention. See, *Ex parte Gould*, 231 U.S.P.Q. 943 (B.P.A.I. 1986). As Bult *et al.* describes

nothing more than a hypothetical reading frame of a yet unknown protein with unknown activity the Bult *et al.* reference is not available as a reference due to the significant lack of enabling disclosure of any kind. Accordingly, Applicants submit that this ground for rejection has been overcome.

REJECTION BASED ON STATUTORY DOUBLE PATENTING UNDER 35 U.S.C. § 101

Claims 1-8, 11-20, 27-40, 41-43 and 46-49 stand rejected based upon Statutory Double Patenting under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-6, 8-19, 26-39, 41-43 and 46-49 of U.S. Patent Application No. 09/282,029.

Applicants respectfully traverse this ground of rejection. In this regard, Applicants respectfully submit that due to the provisional nature of this rejection, it can be more appropriately addressed when the present claims are otherwise in condition for allowance. Additionally, Applicants respectfully submit that the subject claims of U.S. Patent Application No. 09/282,029 are subject to a restriction requirement, and therefore, may be canceled.

Applicants respectfully submit that all of the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If, however, the Examiner has any remaining concerns regarding the allowability of the remaining claims, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

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